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First-ever population-based study on status epilepticus in French Island of La Reunion (France) – Incidence and fatality



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ABSTRACT

Purpose: We aimed to determine the incidence and case-fatality of first-ever status epilepticus (SE) among the general population living in La Reunion Island, a French overseas territory in the Indian Ocean near Madagascar.

Methods: We recruited cases (1st July 2004–30th June 2005) in a population-based manner using neurology, neurosurgery, electroencephalogram, emergency, paediatric and neuroradiology services; emergency medical aid service; emergency and admission service of private and public clinics; neurologists (public and private); private paediatricians and practitioners of various rural hospitals. All cases had an electroencephalogram (EEG) and were assessed by an epileptologist. Standard definition and classification schemes were used. Those with known epilepsy were not part of this analysis.

Results: Sixty-five cases (males: $n = 41$, 63.1%) had epileptologist-confirmed SE, with 38.5% ($n = 25$) being >60 years of age. Global incidence rate was 8.52/100 000 (95% confidence interval 6.5–10.5). A bimodal age distribution with high frequency and incidence among young (<10 years age) (frequency: 12.3%; incidence 6.6/100,000) and aged (>60 years) (frequency: 40.0%; incidence 35.0/100,000) was observed. We found that 60%, 32.3%, 6.7% had convulsive, partial and non-convulsive SE respectively (1% remained unclassified). Of the cases identified, 44.6%, 38.5%, 16.9% had unprovoked, provoked or cryptogenic seizures respectively. The most important aetiological factors identified included: stroke (27.7%), alcoholism/toxicity (18.5%), cryptogenic (16.9%), infections (10.8%). Mortality was 18.5%.

Conclusion: The incidence of SE incidence in La Reunion Island was lower than that described elsewhere. The status type was found to be dependent on aetiology and age. The study confirms that SE is more frequent in men and in older adults and is associated with significant short-term case mortality.

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1. Introduction

Status epilepticus (SE) is a serious neurological condition of prolonged or repetitive seizures and has been investigated in few populations such as UK, Switzerland, and Italy^{1–4} etc. Its incidence varies considerably in prospective (10.3–41/100,000)^{4–6} and retrospective (6.2–18.3/100,000) studies.^{7,8} Thus, in addition to

study-specific differences (e.g. different definition), underlying characteristics of each population could contribute to these differences in incidence rate.³ La Reunion is a French overseas territory and the population here is perceived to be different than in Metropolitan France^{9–12} especially with reference to SE-specific aetiologies including alcoholism, trauma, cerebrovascular event, metabolic abnormalities, infection etc., which together constitute about 50% of SE cases.¹³ In any case, the risk for having SE is said to be higher in non-Caucasians.⁵ These factors suggest that a higher SE incidence could be expected in this population. Furthermore, the risk for high fatality as observed in other populations (immediate and short-term, i.e. during hospitalisation or within 30 days of SE, 7.6–22%) or long-term, within 10 years of initial

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survival after SE, 43%) makes it necessary to evaluate this risk in this population as well.³ So far, there has been no population-based study on SE in La Reunion. We conducted the first study of status epilepticus to prospectively examine the incidence and case-fatality of a first episode of status epilepticus among population of all ages in La Reunion.

2. Methods

2.1. Study area and population

Reunion Island is a tropical French overseas territory ($n = 763,204$, in 2004, 50.9% females) situated in the South Indian Ocean ($55.36^{\circ}\text{E}/21.06^{\circ}\text{S}$) with a total area of $2,512\text{ km}^2$.² It is located about 200 km south west of Mauritius and 9200 km from Paris. The majority of the population is ethnically mixed (53%) or European (23%) and the rest have diverse origins predominantly Indian (Malabars, Muslims, Punjabi etc.) and other minority groups belonging to China and African tribes. The active population works essentially in the tertiary sector and the unemployment rate is 3-fold more (29.5%) than in metropolitan France (8.9%).¹⁴ The level and access to care (practitioners' and specialists') including electroencephalography (EEG), computed tomography (CT), and magnetic resonance imaging (MRI) is of high standards and similar to that in metropolitan France. Reunion Island has four public hospital groups situated in the North (Saint Denis), South (Saint Pierre), East (Saint Benoît), and the West (Saint Paul). The neurology and paediatric services are available in South and North public hospital groups. There is also a private neurology facility in Saint Denis. The Reunion Island is largely urban in nature and only 6% of the population is rural (2009 data).

2.2. Case ascertainment and data management

For this, we conducted a prospective, observational, and multicentre epidemiologic study to identify patients with SE between 1st July 2004 and 30th June 2005. To ascertain all SE episodes as completely as possible during this 1 year period,¹⁵ extensive case collection was done under the auspices of Réunion Association for Research in Neurology, Neurosurgery and Neuropathology; Regional Administration of Sanitary and Social Affairs; Regional Hospital Agency; and French Foundation for Research on Epilepsy and island health authorities of three divisions. Cases were recruited prospectively from neurology services of Saint Pierre hospital (South of Island) and Saint Denis hospital (North of Island); neurosurgery service of Saint-Pierre Hospital; EEG service of Saint Pierre, Saint-Denis et Saint Paul hospitals; emergency, paediatric and neuroradiology services of four primary hospitals; emergency medical aide service; emergency and admission services of clinics; neurologists (eight in public practice and six in private practice); private paediatricians and practitioners of various rural hospitals. The study panel comprised of one neurologist and one epileptologist located in the North and South Hospital groups. A staff meeting was organised every 3 months to manage all included cases. An epileptologist (P. Jallon) coordinated with all EEG laboratories and other neurologists to ensure the completeness of cases who also reviewed all clinical and EEG data. The following were considered as EEG abnormalities: slow waves (local or generalised) and paroxysms (local or generalised). The confidentiality of the data was maintained and the study protocol was pre-approved by the National Committee for the protection of computerised data (Commission Nationale Informatique et Liberté) and the local ethics committee. A written informed consent was obtained from all included cases or their proxies.

2.2.1. Definition and classification of SE

We defined SE as a single clinical seizure lasting $>30\text{ min}$ or repeated seizures over a period of $>30\text{ min}$ without intervening recovery of consciousness.¹⁶ All patients alive $>30\text{ days}$ after onset of SE were regarded as survivors. SE was classified using Treiman Scheme¹⁷ and was classified clinically as convulsive (primary and secondary generalised included), non-convulsive (subtle, typical and atypical absence and complex partial included) and partial (simple partial included) SE.¹⁸ The epidemiological classification included provoked, unprovoked symptomatic and cryptogenic. The classification was performed by an epileptologist based on the clinical and EEG and imaging data.

2.3. Non-inclusion criteria

Patients who had newly-diagnosed unprovoked epileptic seizure lasting $<30\text{ min}$ or febrile, neonatal, or non-epileptic seizures, incomplete medical charts, with known epilepsy, residence outside Reunion Island and diagnosis made outside the study period.

3. Statistical analysis

The incidence (age-, sex-specific) and frequency (age-specific) of SE was calculated. We also calculated frequency of various aetiologies for provoked and unprovoked SE. Confidence intervals 95% (95% CI) were calculated using a Poisson distribution. Analyses were performed with Statview v5.0 software (SAS Institute, Cary, NC, USA). Age-standardised incidence rate was estimated by using direct method to European population. We used 5% statistical significance for statistical calculations.

4. Results

One thousand and six suspected cases of newly-diagnosed unprovoked epileptic seizure were obtained from the island during the study period, 766 had newly-diagnosed epileptic seizure,¹⁵ and a total of 65 cases out of 1006 met the inclusion criteria of being diagnosed as SE. These cases were confirmed by epileptologists.¹⁵ The febrile ($n = 128$), neonatal ($n = 15$), non-epileptic ($n = 46$) seizures, incomplete medical charts ($n = 24$), residence outside Reunion Island and diagnosis made outside the study period ($n = 27$).

4.1. Incidence rate

Sixty five SE cases ($n = 41$, 63.1% males) yielded a global incidence rate of SE of $8.52/100,000$ (95% CI 6.5–10.5) in this population. The age-standardised incidence rate using direct method (to European population) was $10.8/100,000$ (95% CI 8.9–12.9). The sex-specific and age-specific incidence rates are presented in Table 1. Most frequent age-group was 6th decade (23.0%) with a high frequency among those $<10\text{ years}$ and $\geq 60\text{ years}$. Two bimodal incidence peaks were 1st decade ($6.6/100,000$) and 6th decade ($35.0/100,000$), Table 1. The peak of incidence rate was higher in males ($54.5/100,000$) than females ($35.8/100,000$) and was earlier (6th decade) than females (7th decade). The 1st-decade incidence in male children was nearly double ($8.6/100,000$) of that in female children ($4.5/100,000$).

4.2. Classification and aetiologies

Sixty percent (60.0%) had convulsive SE and 32.3% and 6.7% had partial and non-convulsive SE and 1% cases remained undetermined. The epidemiologic classification yielded 44.6% SE cases with unprovoked symptomatic seizures, 38.5% with provoked seizures and 16.9% with cryptogenic seizures. Overall, two major

Table 1

Age and sex-specific incidence (I) rates of status epilepticus.

Age group	Males		Females		Total	
	N	I/100,000	N	I/100,000	N	I/100,000
0–9 years	6	8.6	3	4.5	9	6.6
10–19 years	3	4.2	1	1.4	4	2.9
20–29 years	3	5.3	0	0.0	3	2.6
30–39 years	2	3.4	2	3.2	4	3.3
40–49 years	5	9.6	2	3.7	7	6.6
50–59 years	7	21.1	6	17.6	13	19.3
60–69 years	11	54.5	4	17.6	15	35.0
70–79 years	3	29.4	5	35.8	8	33.1
≥80 years	1	26.8	1	13.1	2	17.6
Total	41	10.9 (95% CI 7.6–14.2)	24	6.2 (95% CI 4.0–8.4)	65	8.5 (95% CI 6.5–10.5)

CI, confidence interval.

aetiological factors were (Table 2): stroke (27.7%) and alcoholism/toxicity (18.5%). For complete picture on aetiologies, please refer to Table 2.

4.3. Management of status epilepticus

4.3.1. Complementary examinations

The EEG was performed in all SE cases. 78.5% had abnormal EEG and it was not interpretable in 7.7% cases, remaining had normal EEG. The CT scan was done in 80.0% of cases and 67.3% had abnormal CT scans of which 3/4th had lesions and 1/4th had no lesions. The Magnetic Resonance Imaging (MRI) of 33.8% cases yielded abnormal findings in 68.2% of cases of which 2/3rd had lesions and 1/3rd had no lesions.

4.3.2. Case locations and diagnostic delay in SE cases

More patients were reported from the Southern centre (Saint Pierre) (61.5%). The diagnostic delay was very short in majority of cases (83.1% within 24 h).

4.3.3. Events as a direct consequence of SE

About 76.9% had no event(s) as a direct consequence of SE. The case-fatality in our cohort was 18.5% whereas 4.6% had a physical injury(s).

4.3.4. Treatment

Phenytoin in 44.6% cases (in combination with benzodiazepine in 69% cases); sodium valproate was used in 30.7% cases (and in combination with benzodiazepine in 75% cases); benzodiazepine in 30.7% cases (monotherapy in 20% cases) and phenobarbital in 15.4% cases (in combination with benzodiazepine in 30% cases). Overall, 84.2% cases were having benzodiazepines as either single or in combination therapy.

5. Discussion

Status epilepticus is a medical emergency that is associated with high mortality. We present here the results of a first

population-based study on status epilepticus in La Reunion that evaluated incidence and case-fatality rates in a population outside Europe or US which makes for majority of studies on SE. We yielded an overall incidence rate of 8.52/100,000 which is lower than rates from other Western populations that ranged from 10.3 to 41.0/1,000,00⁵. In non-western populations, the incidence studies that included both convulsive and non-convulsive forms are rare. Two studies however show a frequency of 11.0% for non-convulsive SE¹⁹ in India, and an incidence of 35.0/100,000 in Kenya.²⁰ The overall SE incidence rate in some black populations may reach 60.0/100,000²¹ which is much higher than that observed in our study. A lower incidence (age-standardised) rate to European population further indicates that the incidence is likely to be lower in Reunion Island than Europe. However we cannot completely ignore the possibility that some proportion of cases might have been missed due to the restricted inclusion criteria we had adopted.

Case ascertainment, and consequently incidence, may be partially influenced by the presence of specialist care²² or under-diagnosis of non-convulsive forms or lack of hospitalisation and clear reporting of seizure duration.²³ Under-ascertainment of cases in our study is less likely since the region is geographically self-contained and good medical facilities are available in close proximities thus loss of cases due to this reason seemed less likely. Use of EEG laboratories as a case-source has been done previously²⁴ and proven to be effective since anyone suspected of having an epileptic seizure would soon undergo an EEG recording to ascertain the diagnosis. However, this ascertainment method is more suitable for populations where such facility is readily available. In any case, we used many case sources that make under case-ascertainment less likely. We had more frequent reporting of SE (61.5%) in South of the Island which could be due to the presence of greater number of reanimation services and the only neurosurgical reanimation service of the La Reunion Island.

Influence of referral bias on incidence estimate seem unlikely since all neurology service-points of the Island were engaged in this study and SE is an emergency situation and it is less likely that patient would not seek any care at all. La Reunion Island has a well

Table 2

Aetiological distribution among status epilepticus cases.

Number	Aetiologies	Unprovoked	Provoked	Total
1	Stroke	n = 16, 40.0%	n = 2, 8.0%	n = 18, 27.7%
2	Alcohol and toxic	n = 6, 15.0%	n = 6, 24.0%	n = 12, 18.5%
3	Cryptogenic	n = 11, 27.5%	n = 0, 0.0%	n = 11, 16.9%
4	Infections	n = 2, 5.0%	n = 5, 20.0%	n = 7, 10.8%
5	Metabolic or autoimmune	n = 3, 7.5%	n = 4, 16.0%	n = 7, 10.8%
6	Cranial trauma, including post-surgical	n = 1, 2.5%	n = 3, 12.0%	n = 4, 6.1%
7	Undetermined or multiple	n = 1, 2.5%	n = 3, 12.0%	n = 4, 6.1%
8	Tumour	n = 0, 0.0%	n = 2, 8.0%	n = 2, 3.1%

developed healthcare service at par with metropolitan France and is likely to be different than other tropical populations where medical care facilities may not be as strong as in La Reunion Island. Furthermore, referral bias due to urban-rural differences is also less likely here as well since the majority of the population of the Island is urban in nature (only 6% are rural).

In our study, 60.0% had convulsive SE and 32.3% and 6.7% had partial and non-convulsive SE. This predominance of convulsive form is well recognised²⁵ and nearly half of the SE cases can be expected to be convulsive in nature although its relative frequency is difficult to establish since various types of status are not specified separately in most series.²⁶ Incidence rate of convulsive SE in African origin population²⁰ is higher than a European population.²⁷ Non-convulsive SE is less frequently reported although it is not rare and could be due to its under-diagnosis since the epileptic nature of the clinical features is not usually readily recognised and EEG may not be available for hours. In studies that included both forms of SE, non-convulsive SE can be observed in 5–6% of cases although frequency up to 23.0% is also reported.³ We yielded slightly higher frequency (~7%) of non-convulsive cases. This variation in frequency could be due to differences in study characteristics³ or due to the fact that diagnosis and EEG was readily conducted in most cases (83.1% within 24 h). It is to note that we had EEG done in all of our cases. Furthermore, the frequency of partial non-convulsive SE is much higher in our study than other populations²⁸ although other studies report that SE of partial onset accounts for the majority of episodes.⁵ However the differences could be due to the difference in distribution of different aetiologies or the observation that in elderly people (as in our study sample), the relative frequency of simple and complex partial forms of SE also increases⁸ and that focal epileptic activity tends to generalise less often in old age.²⁹

While different classification schemes and training of practitioners may introduce bias towards frequency of different SE types, we controlled these by using classic Treiman Scheme¹⁷ that is believed to be more useful than other schemes for emergency treatment decisions; and giving diagnostic and classification task to a very senior epileptologist. Non-convulsive forms are considered to form one-quarter of all SE cases³⁰ and this estimate is not very different in our study.

In our study, as expected, there were age–gender specific differences in the incidence of SE. In general, incidence showed a strong age-dependency⁵ with bimodal distribution and with two peaks at 1st and 6th decade of life. Males (10.9/100,000) had a higher incidence than females (8.52/100,000), which matches with US and some European studies³ but is in contrast to two South European studies² that reported female predominance. This difference could be due to different age–sex composition or higher possibility for stroke, cranial trauma and alcoholism in males or gender difference in seizure threshold or plain hormonal influence in seizure termination.³¹ Our rate of incidence in elderly than in young adults (20–59 years) matches with the observations from other studies.⁵

Furthermore, cerebrovascular disease was the main aetiology (27.7%) in our study which is similarly observed as in other studies³ or metabolic derangement (10.8%) which is less frequent than other populations.²⁸ In contrast to other studies such as in China,²⁸ alcohol-related SE was a common cause in our study and could be due to the lower alcohol consumption and dependence in some communities. This could be another reason for the high frequency of generalised convulsive SE in our study in contrast to other populations.⁷ Idiopathic cases may account for 3–18% of cases²⁸ which was much lower in our study (6.1%) and could be due to the fact that all cases were evaluated, in a timely manner, by very experienced epileptologist and neurologists. Due to number

of factors (e.g. small and isolate geographical area, good medical facilities), the delay in diagnosis and treatment onset was <24 h in most cases in our cases which is often not observed in other large populations²⁸ which may expect a delay in diagnosis in 30% of cases. This is important since delay in reaching hospital (e.g. distance to hospital) may lead to increased duration of SE and consequently high neurological damage and mortality.³²

Treatment may affect outcome by reducing the seizure length and consequential complications. Two studies reported that a significant proportion of patients were not treated prior to arrival to hospital.^{4,6} This is significant, as delayed treatment may increase the frequency of SE³³ and thus could be another reason for low incidence of SE in our population. Benzodiazepines are 1st line treatment in SE cases³⁴ and was used in 84.2% of our cases mostly in combination with other treatments. Even though benzodiazepines are recommended 1st line treatment, it is clinically inadequate for about 1/3rd of cases.³⁴ The significance of efficacy of valproate in treating SE may deserve more detailed evaluation which was beyond the scope of this survey; although valproate can be used in wide range of patient population and SE types.³⁵ It also reportedly has low incidence of side effects.³⁶

SE although was less frequent on this island we experienced a high (18.5%) short-term fatality. This is despite the short diagnostic delay in most case (83.1% within 24 h) and absence of any event(s) as a direct consequence of SE in most (76.9%) of our cases. Our fatality rate is similar to African-American populations elsewhere (17%)⁵ but higher²² or lower than² some Caucasian populations. The short-term mortality (<30 days) in the literature however varies from 7.6 to 33%.³ This high mortality rate could be due to the high proportion of aged population (59%, Table 1) in our sample or could be as a direct consequence of SE since a study showed similar rate of mortality (16%) as a direct consequence of SE.³⁷ Another reason could lie in the nature of aetiologies. Stroke was the major aetiological factor in our study as elsewhere³⁸ and could be a possible factor for high mortality in this population.³⁹ Two studies dealing with SE in stroke patients reported mortality rates of 48.3%³⁷ and 53.0%.⁴⁰ A recent study showed that a relatively poor outcome occurs when the underlying cause is cerebrovascular disease.⁴¹ Moreover, high mortality among SE patients is also associated with organic brain disease⁴² or stroke⁴³ as compared with those patients with no underlying pathology emphasising the possible synergistic effect of SE and a destructive brain lesion such as stroke, alcoholic organic brain disease, infections or cranial trauma as these were significant aetiologies in our study sample as well.

6. Conclusions

We conclude that the incidence of SE in La Reunion Island is lower than that observed in other population-based cohorts. The status type is dependent on aetiology and age and confirms that SE is more frequent in men and the elderly and is associated with a significant short-term case-fatality. Stroke and alcoholism were most important SE-related aetiologies and matches with the high frequency of these disorders in general population. Therefore, patients with stroke should be considered for an EEG in any case of unexplained changes in consciousness. Lastly, expected demographic changes of the population may further influence the incidence of SE in La Reunion Island. SE was predominantly in aged population and it is likely that age-related alterations in renal and hepatic functions, co-morbid conditions or adverse medication effects etc. may have some measurable role to play in facilitating the occurrence of SE. These figures however provide an important baseline for surveillance of this disorder in this population.

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Conflicts of interest

None of the authors has any conflict of interest to disclose.

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